Controlled- and extended-release metoprolol reduced death, hospital admissions, and symptoms in chronic heart failure

Hjalmarson A, Goldstein S, Fagerberg B, et al., for the MERIT-HF Study Group. **Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF).** JAMA. 2000 Mar 8;283:1295-1302.

QUESTION

In patients with symptomatic chronic heart failure, do controlled- and extended-release metoprolol succinate (a β-blocker) reduce mortality, hospital admissions, and symptoms?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessor, {patients, and clinicians}†),* placebo-controlled trial with a mean follow-up of 1 year.

SETTING

313 investigational sites in the United States and 13 European countries.

PATIENTS

3991 patients (mean age 64 y, 78% men) who had had symptomatic heart failure (New York Heart Association [NYHA] class II to IV) for ≥ 3 months, a decreased ejection fraction (≤ 0.40), and a resting heart rate ≥ 68 beats/min and had received optimal treatment for ≥ 2 weeks before randomization. Exclusion criteria included acute myocardial infarction or unstable angina pectoris ≤ 28 days before randomization, indication or contraindication for β₁-blockers, severe decompensated heart failure, or supine systolic blood pressure < 100 mm Hg. Patients with an ejection fraction between 0.36 and 0.40 were excluded if they exceeded 500 yards in a 6-minute walk test. All patients were included in the analysis.

INTERVENTION

Patients were allocated to metoprolol (n = 1990) or placebo (n = 2001). The dose was started at 25 mg/d (12.5 mg/d for patients with NYHA class III or IV) and doubled every 2 weeks until the target dose of 200 mg/d was reached.

MAIN OUTCOME MEASURES

All-cause mortality or any hospital admission, hospitalization for worsening heart failure, and change in NYHA class.

MAIN RESULTS

Analysis was by intention to treat. The study was stopped early because interim analysis showed a 34% reduction in mortality. Fewer patients in the metoprolol group than in the placebo group died or were hospitalized (P < 0.001) or were hospitalized for worsening heart failure (P < 0.001) (Table). Patients in the metoprolol group were more likely to improve by 1 NYHA class (26% vs 24%) or 2 NYHA classes (2.6% vs 1.5%) and were less likely to deteriorate in NYHA class than were patients in the placebo group (P = 0.003 for trend).

CONCLUSION

In patients with symptomatic chronic heart failure, controlled- and extended-release metoprolol reduced mortality, hospital admissions, and symptoms.

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*See Glossary.
†Information provided by authors.

Controlled- and extended-release metoprolol (Met) vs placebo for symptomatic chronic heart failure (HF)‡

Outcomes at mean 1 y	Met	Placebo	RRR (95% CI)	NNT (CI)
All-cause death or hospital admission	32%	38%	16% (9 to 23)	17 (12 to 32)
Hospitalization for worsening HF	10%	15%	32% (19 to 42)	22 (15 to 39)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Our understanding of systolic heart failure in the past decade has evolved through a series of models, from cardiorenal (diuretics), to hemodynamic (inotropic and vasodilator therapy), to the more recent neurohormonal model. The earlier models all achieved the basic clinical need of symptomatic relief, but only the neurohormonal model has addressed morbidity and survival benefits. The earlier conceptual models labeled β-blockade as counterintuitive therapy, but β-blockers are now mandated in conjunction with angiotensin-converting enzyme (ACE) inhibitors in patients who have chronic heart failure with systolic dysfunction.

Even in the face of overwhelming data supporting the use of β-blockers, it is important to apply clinical caution: β-blockade *must not* be begun in the presence of overtly decompensated heart failure; a "start low and go slow" regimen should be followed; close clinical follow-up for signs of decompensation during titration must be maintained; and severe class IV heart failure is usually still a contraindication for β-blockade because of little supportive evidence.

Unlike ACE inhibitors for which a class effect has been shown, different β-blockers still appear to evoke some heterogeneity in their responses. The most validated adrenergic blockers in heart failure include carvedilol, metoprolol CR/XL, and bisoprolol. Little evidence exists for the benefit of other β-blockers in chronic heart failure.

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